REMARKS

Upon entry of this amendment, claims 1-25, 28-43, 47-66, and 68-72 will be pending in this application. Claims 1-18, 21-25, 27, 29-43, 47-66, and 68-71 stand withdrawn as directed to non-elected subject matter. Claim 19 is amended herein without the addition of new matter. Accompanying this response is a request for continued examination, a declaration under 37 C.F.R. §1.132, of Dr. J. Bradford Kline, and declaration exhibits A-H.

Telephone Interview with Examiners Hill and Li

Applicants acknowledge with appreciation the time and courtesies extended by the Examiners toward Applicants' representatives during a telephone interview conducted with Applicants' representatives on July 5, 2007. The Examiners' insights and comments have advanced the prosecution of the case. In particular, the outstanding rejections were discussed, as well as the potential filing of a section 132 declaration. Further discussion involved ways to move prosecution forward in this matter. Applicants would like to note that the Examiners, in an interview summary dated July 11, 2007, have indicated that the written description rejection would be withdrawn.

Objections to the Specification

The drawings stand objected to as allegedly not including a reference sign provided in the description of Figure 4. In a supplemental reply submitted March 21, 2007, Applicants corrected the paragraph numbering to clarify their previous amendments to the specification. It is believed that the supplemental amendments obviate the objection to the drawings. Withdrawal of the objection is requested.

Rejections under 35 U.S.C. § 112, First Paragraph

Written Description Requirement

Claims 19-20 and 28 stand rejected under 35 U.S.C. § 112, first paragraph for allegedly failing to comply with the written description requirement. According to the office action, the specification does not support the full genus of AAT and EMAP genes claimed, does not support the scope of claimed methods for suppressing AAT and EMAP expression,

and does not support the genus of AAT and EMAP targeting vectors. To the extent the rejection would be maintained against the amended claims, Applicants disagree.

The specification, coupled with the knowledge available in the art in 2003 adequately describes the structural and functional aspects of the claimed genus, including the AAT and EMAP genes, such that those of skill in the art would understand that the Applicants were in possession of the full scope of the amended claims. Applicants are submitting herewith a Declaration under 37 C.F.R. § 1.132 of Dr. J. Bradford Kline as evidence of the level of knowledge in the art regarding AAT and EMAP genes, and the tools and techniques available to practice the invention as of the application's filing date.

With respect to the structural aspects of the invention, the specification discloses the sequences of murine alpha-1-antitrypsin and endothelial monocyte-activating polypeptide I, and the sequences of AAT and EMAP were known and identified in the art for species such as human, chimp, mouse, and rat as of 2003. See, Kline Declaration, paragraph 11. In fact, AAT homologs from hamster, human, rabbit, rat, and sheep, and EMAP homologs from rabbit, dog, human, rat, and pig are provided in paragraph 0072 of the disclosure. Therefore, the structures of the claimed genes were known and readily available to those of ordinary skill in the art. Furthermore, because the AAT and EMAP families are relatively small, the disclosed species represent a sizable proportion of the genus of AAT and EMAP genes. Thus, the specification and established knowledge in the art demonstrate that the structural aspects of the claimed invention are adequately provided for in the instant application.

With respect to the functional characteristics of the claimed invention, it is noted that the suppression of AAT or EMAP genes in an antibody producing cell enhances the titer of antibodies produced. This effect was demonstrated by diverse means of gene suppression as described in paragraphs 0073 through 0078 of the specification (AAT/EMAP gene suppression by antisense, protease inhibitors, and antiserum each showed enhanced antibody titer in antibody producing cells). The functional aspects of the claimed methods and vectors could be readily screened using any method suitable in the art, including those described in the specification. See, *e.g.*, Example 2. Thus, it is submitted that the functional aspects of the claimed invention are adequately described in the specification such that one of ordinary skill in the art would have understood that Applicants were in possession of the full scope of the invention as claimed.

The office action also alleges that there is insufficient description of knock-out targeting vectors for AAT/EMAP gene disruptions. Applicants respectfully disagree. Gene knockout technology was sufficiently established in the art at the time of filing such that, on the basis of the information provided in the specification, coupled with what was known in the art about the sequence of the AAT and EMAP genes and their respective upstream and downstream sequences, one of ordinary skill in the art would understand that the Applicants were in possession of the claimed genus of AAT and EMAP knockout vectors and methods for performing AAT and EMAP knockout. For example, given that the AAT and EMAP genes of many species were known and characterized in the art (specification at 0072, and Kline Declaration, paragraph 11), it was well within the skill of the art to identify the AAT and/or EMAP genes, design knockout vectors for those genes, and perform AAT and EMAP knockout. In light of the disclosed sequences and the high level of skill in the art, identification of the other members of the AAT and EMAP families and production of knockout vectors for those genes would have been straightforward. For example, the scientific literature was replete with examples of different vectors and techniques that could be utilized, and many vectors and knockout kits were commercially available. (See, Kline Declaration, paragraph 7) Any such vectors could have been easily modified for use against AAT and EMAP genes as claimed.

As the foregoing discussion indicates, the structural and functional aspects of the claimed genes and knockout methods are provided by the specification and the well-established knowledge in the art. In addition, a wide array of knockout vectors and tools were available, such that knockout vectors could be easily produced and utilized in the present invention. Thus, those of ordinary skill in the art would understand that Applicants were in possession of the full scope of claimed knockout methods and knockout vectors. Accordingly, the claims are adequately described, and reconsideration and withdrawal of the rejection is requested.

Enablement Requirement

Claims 19-20 and 28 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification. According to the office action, the specification does not enable AAT or EMAP gene knockout because the art did not consider knockout

phenotype to be predictable at the time of the application's filing and the application does not adequately disclose the starting materials necessary for performing the invention. Applicants disagree with this rejection.

With respect to the issue of the predictability of gene knockout techniques generally, Applicants submit that the technology was sufficiently predictable at the time of the application's filing such that one of ordinary skill in the art could routinely perform gene knockout. Dr. Kline's Declaration demonstrates that the field of gene knockout was so well established in 2003 as to remove any reasonable doubt that AAT and/or EMAP-knockdown cells could be produced based on the instant disclosure without undue experimentation. For example, Dr. Kline has explained that thousands of articles and numerous books described gene knockout methods as of 2003. See, Kline Declaration, paragraphs 6-8. Moreover, gene knockout technology was so advanced and routine that it was regularly taught and practiced in the laboratory portion of college biology courses. See, Kline Declaration, paragraph 12. Given that detailed protocols for performing gene knockout were readily available and routinely practiced as of the instant application's filing date, those of ordinary skill in the art would have had a reasonable expectation that AAT and/or EMAP genes could be successfully knocked out in an antibody producing cell of interest, with a reasonably predictable result.

Regarding the predictability of gene knockout phenotype, the AAT and EMAP antisense studies described in the instant disclosure provide sufficient basis to predict AAT and EMAP gene knockout phenotype. In the first instance, an antisense-knockdown phenotype generally correlates with its respective knockout phenotype. See, Kline Declaration, paragraph 28. Thus, those of skill in the art would reasonably expect that the AAT and EMAP antisense phenotypes would also be observed in cells in which these genes have been knocked out. Indeed, several methods used for antisense studies overlap with those of gene knockout. For example, antisense transcripts and gene knockout vectors are designed in a similar manner and contain many of the same components. In addition, many methods for targeting antisense transcripts and knockout vectors to the genome are the same. Furthermore, both antisense transcripts and knockout vectors contain positive and negative selection markers to enable screening for proper vector incorporation in a similar manner. Additionally, antisense and gene knockout utilize the same methods to confirm gene product

suppression. Given this substantial overlap, the Applicants' success with antisense is highly predictive of success with AAT and EMAP gene-knockout. In addition, AAT and EMAP knockout would not be expected to be lethal. See, Kline Declaration, paragraph 27.

Second, because the AAT and EMAP genes are relatively small, knockout of these genes is more straightforward than for larger genes, and thus the likelihood of forming the desired phenotype is high (this was no less true in 2003). Gene knockout tends to be more straightforward for genes that are relatively small (< 20 kb) because the entire gene can be deleted through gene knockout. See, Kline Declaration, paragraph 26. In contrast, for larger genes, some portion of the gene can sometimes remain. Thus, when the entire gene is deleted, there is a lower likelihood of expressing at least some gene products, and therefore, the expectation of successful knockout is increased. See, Kline Declaration, paragraph 26.

Third, there is no expectation of functional redundancy for AAT or EMAP gene products. On this basis, those of skill in the art would expect that knockdown of AAT and/or EMAP would yield the desired phenotype. Applicants have demonstrated that down-regulation of AAT and EMAP is correlated with the desired phenotype (increased antibody production). See, Kline Declaration, paragraph 29, and paragraphs 0073-0078 of the specification. There is no mention or suggestion in the scientific literature of functional redundancy for AAT or EMAP. See, Kline Declaration, paragraphs 31 and 32. Therefore, there is no reason to believe that the observed AAT and EMAP antisense phenotypes would not be predictive of the AAT and EMAP knockout phenotypes. In other words, even if an extant additional AAT or EMAP gene were present, or another gene were to compensate for the loss of the knocked out AAT and/or EMAP gene, there is no reason to expect that the net effect of enhanced antibody expression would not occur. Moreover, the instant application does not seek to determine the functions of AAT or EMAP, but instead is directed toward producing a particular phenotype known to be associated with their suppression. Any secondary phenotypical changes occurring in addition to the desired phenotype are not relevant to the issue of whether antibody expression is increased in the cells in which these genes are knocked out. In addition, because the claimed invention is practiced in cells *in vitro*, any incidental secondary phenotypical changes that might be expected to impact, for example, a transgenic animal, would be expected to be less problematic.

As the foregoing discussion indicates, the phenotype of AAT and/or EMAP knockout in an antibody producing cell would be recognized as reasonably predictable by those of skill in the art. This is particularly true in light of the observations made with antisense-based AAT and EMAP knockdown in antibody producing cells, and in light of the lack of apparent functional redundancy among these genes.

Moving next to the issue of starting materials, the instant application in fact provides the starting materials necessary for practicing the claimed invention. As concerns the techniques for producing knockout cells, there were thousands of articles and numerous textbooks providing specific protocols for gene knockout, and for recombinant DNA techniques in general. See, Kline Declaration, paragraphs 6-7. In fact, dual and triple knockdown cells were readily produced using techniques such as sequential targeting. See, Kline Declaration, paragraph 36. Given the advanced state of the art of gene knockout, it is not necessary that the specification detail techniques for producing a knockout. Dr. Kline's declaration at paragraphs 9-25 provides an overview of the techniques at the disposal of the skilled artisan as of 2003.

With respect to the components of the knockout vectors themselves, the sequences of AAT and EMAP genes, along with their upstream and downstream sequences, were known and publicly available as of 2003 for multiple species, including: human, chimp, mouse, hamster, rabbit, sheep, dog, pig, and rat. See, Kline Declaration, paragraph 11, and specification paragraph 0072. Vectors, reagents, laboratory equipment, antibody producing cells and cell lines, and the like were all publicly or commercially available. Those of skill in the art would be expected to select the vectors, reagents, and cells appropriate for their particular skill level and needs. Thus, it is submitted that all of the pieces necessary to construct knockout vectors are provided for by the specification and the knowledge and skill in the art. Even if a large amount of experimentation were required to produce an appropriate knockout vector, and Applicants are not conceding or suggesting that it would be, such experimentation would be routine, and by definition, not undue.

In support of this latter point, Applicants submit that the specification provides a roadmap, based in part on Applicants' antisense, small molecule, and antiserum knockdown experiments, for those of skill in the art to use to produce AAT and/or EMAP knockdown antibody producing cells. For example, as explained above, many of the starting materials

used for AAT and EMAP antisense studies could also serve as starting materials for AAT and EMAP knockouts, thereby further reducing the amount of experimentation required to produce successful knockouts. See, Kline Declaration, paragraph 34. In fact, it is generally thought that gene knockout is more straightforward than antisense, which was successfully performed by Applicants. See, Kline Declaration, paragraph 34. Thus, because the genetic sequences of AAT and EMAP were known, the protocols for gene knockout were well established, and antisense and gene knockout have many starting materials in common, the instant application adequately discloses the starting materials necessary to perform AAT and EMAP knockout as of 2003 such that the invention could be practiced without undue experimentation.

Moving next to the issue of the feasibility of constructing specific AAT and EMAP knockout vectors, Applicant's submit that specific structural disclosure of AAT and/or EMAP knockout vectors was not necessary for those of ordinary skill in the art to practice the invention. The office action states that there is a lack of evidence in the prior art suggesting a link between AAT expression and antibody suppression. Applicants present evidence, however, of a link between AAT and EMAP down-regulation and the desired phenotype (increased antibody production). See, Kline Declaration, paragraph 30. Because the phenotype is correlated with AAT and EMAP down-regulation, and those of ordinary skill in the art could produce the desired phenotype using AAT and EMAP knockout without undue experimentation, a structural disclosure of the AAT and EMAP knockout vectors is not necessary to fully enable the claimed methods.

In the same vein, because the desired phenotype was known, screening for AAT and EMAP knockout would not have required undue experimentation from those of ordinary skill in the art. The specification provides a specific phenotype (increased antibody production) for which cells could be screened. Screening for increased antibody production in transfected cells versus non-transfected cells would have been straightforward. Indeed, numerous means are at the disposal of the skilled artisan to measure increased antibody expression. The technique chosen is not critical, and can vary with the needs or skill of the particular investigator.

In addition to screening cells for increased antibody production, other methods are available in the art to enable one to screen for successful gene knockout as indicated by

proper knockout vector incorporation. Positive selection markers such as neomycin phosphotransferase and negative selection markers such as herpes simplex virus thymidine kinase could have been incorporated into knockout vectors to verify proper vector incorporation. See, Kline Declaration, paragraphs 15 and 16. Moreover, reporter genes such as GFP could have been incorporated with the knockout vector to provide visual evidence of vector incorporation.

As the foregoing discussion demonstrates, the instant specification, coupled with the well established knowledge and skill in the art, provides the necessary starting materials and a roadmap for making antibody-producing cells having AAT and/or EMAP genes knocked out with the result of enhanced antibody expression. In addition, the antisense experiments described in the specification are recognized as being reasonably predictive of the phenotype of an AAT/EMAP knockout antibody-producing cell. Given the advanced state of the art of knockdown technology, those of skill in the art would be expected to be able to practice the claimed invention using routine techniques without undue experimentation. Applicants request reconsideration of the rejection in light of Dr. Kline's opinion, provided in support of the arguments made herein.

Conclusion

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicants request entry of the foregoing amendments, and reconsideration and withdrawal of the various objections and rejections. A Notice of Allowance is earnestly requested.

Respectfully Submitted,

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